

Remarks

Withdrawal of All Previous Rejections

The withdrawal of all previous rejections under 35 U.S.C. 112 is greatly appreciated.

Rejections of Claims over the Prior Art

Claims 1-4 and 6-10 were rejected under 35 U.S.C. §103 as obvious over Skraly,

Polyhydroxyalkanoates Produced by Recombinant *E. coli*, Poster Engineering Foundation Conference: Metabolic Engineering 1998 ("Sklary"), Madison, et al. Metabolic engineering of poly(3-hydroxyalkanoates): from DNA to plastic. *Microbiol. Mol. Biol. Rev.* 63(1):21-53 (1999) ("Madison") and BRENDA database ("Brenda database"). This rejection is respectfully traversed.

The Legal Standard under 35 U.S.C. § 103

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). Furthermore, the "[d]etermination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). Rather, there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select

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particular elements, and to combine them as combined by the inventor. *See Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); *ATD Corp.*, 159 F.3d at 546, 48 USPQ2d at 1329; *Heidelberger Druckmaschinen AG v. Hartscho Commercial Prods., Inc.*, 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination."). As stated in *In re Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000):

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See [*In re Dembiczak*, 175 F.3d 994 at 999, 50 U.S.P.Q.2d [1614] at 1617 [Fed. Cir. 1999]. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." *Id.* (quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983)).

The Claimed Subject Matter

Independent claims 1 and 10 define a method for producing and a system for making, respectively, polyhydroxyalkanoates comprising providing organisms selected from the group consisting of bacteria, plants, and yeast (see at least page 5, lines 18-21), which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, {45072764.1} 6

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acetoacetyl-CoA reductase, and PHA synthase (see at least page 5, lines 1-5), wherein the organisms are genetically engineered to express polynucleotides that encode enzymes (see at least page 3, lines 15-18), which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase (see at least page 4, lines 2-3, page 5, line 18 to page 6, line 28 and Examples 4 and 6), wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate (see at least page 2, line 22 to page 3, line 6 and claims 11 and 21 as originally filed), and culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da (see at least claims 1 and 11 as originally filed, page 4, lines 14-16 and the Examples).

Dependent claims 2, 3, 4, 6 and 7 define the diol as 1,6-hexanediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol and 1,2-propanediol, respectively and the hydroxyalkanoate monomer as 6-hydroxyhexanoate, 5-hydroxyvalerate, 4-hydroxybutyrate, 2-hydroxyethanoate and 2-hydroxypropionate (see at least page 2, line 25 to page 3, line 3). Dependent claim 8 defines the method of claim 1 wherein the organism expresses polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase (see at least page 4, lines 2-3). Dependent claim 9 defines the method of claim 8 wherein the organism is selected from the group consisting of

Escherichia coli, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., and {45072764.1}

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Comamonas spp. (see at least claim 9 as originally filed, page 1, lines 16-21, page 3, lines 18-22, page 5, lines 6-7 and page 6, lines 13-17).

The claims of the present application define methods and system for producing polyhydroxyalkanoates comprising providing organisms with polynucleotides that encode enzymes, which are active in bacteria or plants, selected from diol oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers.

The Applicants have provided working examples which demonstrate that one can use the claimed enzymes to engineer organisms to produce polyhydroxyalkanoates from diols, such as 1,4-butanediol (see Examples 3, 4 and 7) and 1,3-propanediol (see Examples 5 and 6).

The Prior Art

Skraly

Skraly is a review of methods for genetically engineering organisms to make a variety of different PHAs. Page 7 indications that 1,3-propanediol and 1,5 pentanediol can be used as feedstocks to make p(3HP) and P(3HP-co-5HV) (page 7). At page 9 there is a reference to using a 1,3-propanediol oxidoreductase to synthesize PHB-co-3HP from glycerol and PHB-co-3HV from 1,2-propanediol.

Madison

Madison is a review. The examiner is correct that Madison does not disclose the claimed elements. Nor is there any teaching leading one to conclude that one should, or could make the claimed organisms and produce polymers from the claimed monomers. Madison does teach one {45072764.1} 8

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that PHAs made by bacteria can have a low, mid or high molecular weight. This is a far cry from a teaching that one should start with diols not described in any of the references, use enzymes not described in any of the references, and expect to make high molecular weight PHAs as claimed.

Analysis

The examiner has done an excellent job of taking the claims in issue, then searching for prior art that discloses some of the claimed elements, then concluding that since they all generally relate to making polyhydroxyalkanoates, that it is obvious to combine. This is not an appropriate analysis under 35 U.S.C. 103. The art must disclose each claimed element, and the motivation to combine, with a reasonable expectation of success. The examiner has failed to demonstrate where in the cited art the motivation may be found. One cannot use hindsight.

Claim 1 recites:

A method for producing polyhydroxyalkanoates comprising
providing organisms selected from the group consisting of bacteria, plants, and yeast,
which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-
CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase, and PHA synthase,
wherein the organisms are genetically engineered to express polynucleotides that encode
enzymes, which are active in bacteria or plants, selected from the group consisting of *diol*
oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms
can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-
hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-

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hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate,
and

culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

Skraly does not disclose a system that can convert diols into hydroxyalkanoate monomers selected from the group consisting of **4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate**. The only monomers that Skraly describes using are PHB-co-3HP (from 3-hydroxybutyrate and 3-hydroxypropionate) and PHB-co-3HV (from 3-HB and 3-hydroxyvalerate). None of these are claimed. The examiner has drawn conclusions that one could read into the disclosure that other diols could be utilized, but no evidence for such a conclusion is found in the reference, much less what enzymes would be required and whether they would have the appropriate specificity. There is no basis to conclude that one would make the substitutions in feedstock that applicants have done, to produce the claimed polymers, based on this disclosure. Indeed, it was two years later that applicants, who worked with Skraly, et al., filed this application, having isolated the necessary materials, engineered the cells and demonstrated that it was possible.

Madison, as noted above, does not make up for these deficiencies. No where is there any teaching that one could or should make a high molecular weight PHA from diols converted into the claimed monomers. The examiner has not even identified where such polymers are

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described. Even as to the molecular weight range, this is not for polymers of the claimed monomer composition, but conventional PHB polymers.

The Brenda database does not make up for this. Applicants have told those skilled in the art how to practice their claimed method; the standard is not whether having the answer in hand one can support the conclusion. This is the examiner's approach, however.

One also cannot just "lump" the claims together, focusing solely on the elements in the independent claims, and completely fail to examine the elements of the dependent claims. This is as unacceptable as using hindsight.

None of the specific diols and monomer compositions of the following claims is at all described in the prior art cited by the examiner:

Claim 2, wherein the diol is 1,6-hexanediol and the hydroxyalkanoate monomer is 6-hydroxyhexanoate.

Claim 3, wherein the diol is 1,5-pentanediol and the hydroxyalkanoate monomer is 5-hydroxyvalerate.

Claim 4, wherein the diol is 1,4-butanediol and the hydroxyalkanoate monomer is 4-hydroxybutyrate.

Claim 6, wherein the diol is 1,2-ethanediol and the hydroxyalkanoate monomer is 2-hydroxyethanoate.

Claim 7, wherein the diol is 1,2-propanediol and the hydroxyalkanoate monomer is 2-hydroxypropionate.

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In summary, the prior art neither discloses the claimed elements nor the motivation to combine as applicants have done, much less with a reasonable expectation of success.

For the foregoing reasons, claims 1-4 and 6-10 are patentable.

Respectfully submitted,

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Date: December 26, 2006

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